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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,881	12/10/2001	Manfred Reiter	V-260.00	2884

7590 01/28/2004

Bexter Healthcare Corporation
P. O. Box 15210
Irvine, CA 92614

EXAMINER
CHEN, STACY BROWN

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,881	REITER ET AL.	
	Examiner	Art Unit	
	Stacy B Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-19,21 and 24-38* is/are pending in the application.

4a) Of the above claim(s) *24-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7-7-2003* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendment filed November 17, 2003 is acknowledged and entered. Claims 1-9, 11-19, 21 and 24-38 are pending. Claims 1-9, 11-19 and 21 are examined. Claims 24-38 are withdrawn from consideration, being drawn to a non-elected invention.

Response to Amendment

2. Claim 6 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 recites improper Markush language. Proper Markush language is "selected from the group consisting of ... and ...". Claim 6 currently recites "selected from the group consisting of ... or ...". Appropriate correction is required.

Response to Arguments

3. The rejection of claims 1-5, 7, 8 and 10-13 under 35 U.S.C. 102(b) as being anticipated by Giroux *et al* (5,994,134) is withdrawn in view of Applicant's persuasive arguments. The rejection of claims 6, 9 and 14-21 under 35 U.S.C. 103(a) as being unpatentable over Giroux *et al* (5,994,134) as applied to claims 1-5, 7, 8 and 10-13, and further in view of Webster *et al* (6,344,354) and Gröner *et al* (6,455,298) is withdrawn in view of Applicant's persuasive arguments. Applicant's substantive arguments were primarily directed to the Giroux reference, which fails to teach the method step of increasing cell density during or prior to infection with virus. In response, the Office withdraws the prior art rejections of record. Upon further consideration of the claims under examination, the following new grounds of rejection are made:

Claim Rejections - 35 USC § 102

4. Claims 1, 2, 4, 5 and 11-12 are rejected under 35 U.S.C. 102(b) as anticipated by Caij *et al* (*Arch Virol.*, 1989, 105:113-118), cited in the information disclosure statement of February 20, 2003. The claims are drawn to a method of producing virus or viral antigen comprising culturing cells bound to a microcarrier, grown to confluence, infected with virus, incubated, and finally harvested and purified. The cell density of the biomass of the cell culture is increased before or after infection, and maintained during incubation. The microcarrier can be made of dextran and used in a concentration between about 0.5 g/L and about 14 g/L.

Caij teaches a method of producing Hog Cholera virus on microcarrier cultures using PK-15 cells (abstract). Caij uses dextran-based beads in the amount of 0.5 to 14 g/L (page 116, first paragraph). Caij's method comprises culturing cells bound to a microcarrier, grown to confluence, subsequently scaling up culture volumes prior to infection, infecting, incubating, harvesting and purifying viruses (page 115). The process of scaling up the culture volumes involves subpassaging, wherein cells become detached from the microcarriers and are pelleted down, then resuspended in growth medium and used for inoculating greater numbers of microcarriers (page 115, third full paragraph). Caij's method is intended for increasing virus titer by reducing the volume of growth medium. The result of reducing growth medium would extend beyond increased virus titer to increased cell density (page 113, last full paragraph). Caij increases the number of cells and the microcarrier concentration to achieve a maximum yield (page 115, next to last paragraph). In a comparison with the traditional method of culturing HCV in PK-15 cells, Caij shows an increase in HCV titer by more than 1.5 log using the microcarrier culture method (pages 116-117, bridging paragraph).

Claim Rejections - 35 USC § 103

5. Claims 3, 6, 7-9, 13-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caij *et al* (*Arch Virol.*, 1989, 105:113-118) as applied to claims 1, 2, 4, 5 and 11-12 above, and further in view of Kessler *et al* (*Dev. Biol. Stand.*, 1999, 98:13-21) and Merten *et al* (*Dev. Biol. Stand.*, 1999, 98:23-37), all of which are cited in the information disclosure statement of February 20, 2003.

Caij is silent on the particular cell lines instantly claimed, and the density of the cells of between about $0.6x10^6$ and $7.0x10^6$ cells/mL. Caij fails to teach a microcarrier culture system wherein serum free and/or protein free media is used. Caij fails to teach the production of influenza virus.

However, Kessler discloses a method of producing influenza virus in MDCK cells in the absence of serum containing medium (abstract). The cells are grown on microcarriers to a density of $1.8\text{-}2.7x10^5$ cells/cm^2. Merten teaches production of influenza virus in serum-free microcarrier cell cultures using VERO and MDCK cells (abstract).

It would have been obvious to incorporate the particulars of the methods of Kessler and Merten into the method taught by Caij. One would have been motivated to produce influenza into Caij's method because Caij produces large amounts of viral antigen (HCV) uses the same culture system commonly used for producing influenza virus. Caij's method increased viral titer by reducing growth medium. One would have been further motivated to use Caij's method to produce influenza viral antigens given the long-felt need for large-scale production of influenza

virus for immunization, as evidenced by annual immunizations against influenza world-wide which are often accompanied by vaccine shortages. One would have had a reasonable expectation of success that influenza virus would have been successfully produced in Caij's method since the method is well known for producing large amounts of viral antigen, as evidenced by Kessler and Merten who use microcarriers to produce their influenza viruses/antigens. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

In the amendment dated November 17, 2003, Applicant argues that the claimed method has unexpected results, namely, that increased cell density was not expected to increase viral yield. In response, while increased cell density may have been expected to ultimately reduce viral yield, Caij shows that increased cell density increased viral yield. Therefore, in view of Caij's teachings, the instantly claimed method did not have unexpected results, but resulted exactly as Caij taught.

Conclusion

6. No claim is allowable.

Papers relating to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 located in Crystal Mall 1. The Fax number for Art Unit 1648 is (703) 872-9306. All Group 1600 Fax machines will be available to receive transmissions 24 hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Stacy B. Chen, whose telephone number is (703) 308-2361. The Examiner can normally be reached on Monday through Friday from 7:30 AM-4:00 PM, (EST). If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, James C. Housel, can be reached at (703) 308-4027. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SBC
Stacy B. Chen
January 16, 2004

James C. Housel 1/26/04
JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600